REMARKS

Status of the claims

Claims 15-38 are pending in the application. Claims 26-38 are withdrawn from consideration and herein canceled. Claims 15, 18 and 19 are currently amended. Claims 16-17 and 20-25 are herein canceled. Claims 15-25 are rejected. No new matter is added.

Claim amendments

Claim 15 is amended to incorporate the terms "risk of bone disease characterized by bone loss". This claim is further amended to recite "the human homologue of Dickkopf-1 (DKK1) protein" and delete the terms "WNT signaling antagonist". These amendments are incorporated to overcome claim rejections under 35 USC §112, first paragraph. Claim 18 is amended to delete "PCR assays or" to overcome the objection to this claim for reciting non-elected subject matter. Claim 19 is amended to recite "wherein said individual has multiple myeloma" and delete "osteoporosis, post-menopausal osteoporosis and malignancy-related bone loss". Claims 16-17 and 19-25 are herein canceled to overcome rejections under 35 USC §112, first paragraph. No new matter is added.

Claim Objections

Claims 16, 17 and 18 are objected to because they recite non-elected subject matter. Claims 16 and 17 are herein canceled. Claim 18 is

amended to delete non-elected subject matter as described above. Accordingly Applicant respectfully requests that the objection of claims 16, 17 and 18 be withdrawn.

Claim rejection under 35 USC §112

Claims 15, 17-20 are rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. Applicant respectfully traverses this rejection.

The Examiner states that the claims include a genus of compounds referred to as "WNT signaling antagonist". The Examiner further states that the written description in the instant application only describes two species of WNT signaling antagonist, i.e., soluble frizzled related protein 3 (SFRP-3/FRZB) or the human homologue of Dickkopf-1 (DKK-1).

Applicant submits that claim 15 is amended to recite only one WNT signaling antagonist, the human homologue of Dickkopf-1 (DKK-1) as per the restriction requirement. The claim is further amended to delete the broadly claimed genus of compounds referred to as "WNT signaling antagonist". The specification provides examples (Table 2, Figure 1B,Example 8 and Example 9), which clearly indicate significant upregulation of DKK-1 in individuals with multiple myeloma accompanied with lytic bone lesions as compared to individuals with multiple myeloma but with no bone lesions (lesions not detected by bone MRI and X-ray). Thus, the specification clearly indicates that there is a specific correlation between significant upregulation of DKK1 and bone disease

in multiple myeloma. As claims 18 and 19 are dependent on claim 15, these claims thereby incorporate all the limitations of claim 15. In view of the amendments, claim 15, 18 and 19 recite subject matter adequately described in the specification. Claims 16-17 and 20 are herein canceled. Accordingly, Applicant respectfully requests that the rejection of claims 15 and 17-20 under 35 USC § 112, first paragraph, be withdrawn.

Claims 15-25 are rejected under 35 USC § 112, first paragraph, as failing to comply with the enablement requirement. Applicant respectfully traverses this rejection.

The Examiner states that the instant specification teaches diagnosis of bone disease in a multiple myeloma patient comprising comparing the level of DKK-1 expression in an individual with multiple myeloma to that expressed in a "normal" individual. The Examiner states that the specification appears to be silent on how to interpret this as a method of determining the risk of developing any and/or all bone disease. The Examiner further states that the risk of cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and monitored over some period of time prior to the disposition of cancer. The Examiner also states that a combination of **Chappuis** et al. (Cancer Treat Res. 2002; 107: 29-59) and **Mclaughlin** et al. (Tannock, I.F. and Hill, R.P., The basic Science of Oncology, Chapter 2, (3rd Ed., 1998)) teaches that genetic factors and environmental factors serve as determinants for cancer risk in a population. The Examiner contends that the

instant specification does not provide any models or experimental analysis that suggest the claimed method would predictably determine the risk of the development of bone disease in an individual. Applicant respectfully disagrees.

Applicants submit that claim 15 is amended to recite determining risk of a bone disease characterized by bone loss in an individual. The claim reads on "risk of developing a bone disease" and not risk of developing cancer as is referred to in the teachings of **Chappuis et al**. and **Mclaughlin et al**. The claim recites a logical conclusion inferred from experimental analysis as explained below.

DKK-1 specifically inhibits canonical WNT signaling by binding to LPR5/LRP6 component of the functional WNT receptor complex. The prior art has identified that gain of function mutations in LRP-5 is linked to a high bone mass phenotype. It is further known that DKK-1 inhibition is defective in the presence of such mutations and that this results in increased WNT signaling. Thus, the increase in WNT signaling mediated by decrease in DKK-1 inhibition results in higher osteoblast activity leading to high bone mass. Furthermore, it has been demonstrated that targeted disruption of LRP-5 gene, in a mice model, results in a low bone mass phenotype (pgs. 19-23). One can logically conclude from above, that if the level of DKK-1 expression increases then there would be low osteoblast (bone formation) activity due to a concomitant decrease in WNT signaling. Thus, an individual exhibiting higher levels of DKK-1 protein would be at a high risk of developing a bone disease characterized by bone loss as a result of low osteoblast activity that is mediated via the WNT signaling pathway.

Applicants submit that Example 17 further provides important data on the role of DKK-1 in osteoblast differentiation. Bone morphogenic protein-2 can induce differentiation of uncommitted mesenchymal progenitor cell line, C2C12, into osteoblats through a mechanism that involves WNT/β-catenin signaling. Alkaline phosphatase, a specific marker of osteoblast differentiation was inhibited in C2C12 cells cultured with BMP-2 and bone marrow serum with a DKK-1 concentration >12 ng/ml (from donors with multiple myeloma). This inhibition was also observed in the presence of 50 ng/ml of recombinant human DKK-1. A reversal of alkaline phosphatase inhibition was observed in the presence of anti-DKK-1 antibody. The inhibition of alkaline phosphate was not seen when the bone marrow serum from a normal donor was used (Figure 41B). This clearly demonstrates the inhibitory effect of DKK-1 on osteoblast activity. Furthermore examples 8 and 9 adequately demonstrate the higher upregulation of DKK-1 in individuals with multiple myeloma accompanied by lytic lesions as compared to individuals with no bone lesions. Even though lytic lesions were observed in patients with multiple myeloma, as high levels of DKK-1 in general inhibits osteoblast activity it is fair to conclude that individuals with upregulation of DKK-1 are at risk of developing a bone disease characterized by bone loss.

Applicant submits that the detailed experimental analysis provided in the specification, as explained supra, clearly indicate that very high upregulation of DKK-1 will result in a bone disease characterized by loss of bone mass. Establishing the presence of a specific risk factor such as over expression of DKK-1 in individuals provides suitable clinical guidelines to delay if not

eliminate onset of such bone related diseases. Applicant submits that in view of the arguments presented above, it is clear that over expression of DKK-1 in an individual presents a risk that this individual will develop a debilitating bone disease. Thus, Applicant submits that the amended claims 15 and 18 recite subject matter that is enabled by the instant specification. Claim 19 recites DKK-1 upregulation related risk of bone disease in an individual with multiple myeloma, which as explained supra is supported by the specification. Claims 16-17 and 20-25 are herein canceled. Accordingly, Applicants requests that the rejection of claims 15-25 under 35 USC §112, first paragraph, be withdrawn.

This is intended to be a complete response to the Office Action mailed August 10, 2005. Applicants submit that claims 15, 18 and 19 are in condition for allowance and respectfully request that claims 15, 18 and 19 be passed to issuance. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution. Should any fees be due, please debit Deposit Account No. 07-1185 upon which the undersigned attorney is allowed to draw.

Respectfully submitted,

Date: Oct 7, 2005

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